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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/00, 47/00	A1	(11) International Publication Number: WO 90/08537 (43) International Publication Date: 9 August 1990 (09.08.90)
(21) International Application Number: PCT/US90/00721 (22) International Filing Date: 6 February 1990 (06.02.90) (30) Priority data: 307,385 6 February 1989 (06.02.89) US (60) Parent Application or Grant (63) Related by Continuation US 307,385 (CIP) Filed on 6 February 1989 (06.02.89) (71) Applicant (for all designated States except US): ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).	(72) Inventors; and (75) Inventors/Applicants (for US only) : ADJEI, Akwete, L. [US/US]; 38770 Red Oak Terrace, Wadsworth, IL 60083 (US). CHESKIN, Howard, S. [US/US]; 893 Valley Road, Glencoe, IL 60022 (US). VADNERE, Madhu, K. [IN/US]; 221 N. Fiore Parkway, Vernon Hills, IL 60061 (US). BUSH, Eugene [US/US]; 305 Kenloch, Libertyville, IL 60048 (US). JOHNSON, Edwin, S. [US/US]; 1037 Main Street, Antioch, IL 60002 (US). (74) Agents: GORMAN, Edward, Hoover, Jr. et al.; Abbott Laboratories, Chad-0377, AP6D/2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>	
(54) Title: PHARMACEUTICAL COMPOSITIONS FOR ORAL ADMINISTRATION (57) Abstract Improved oral formulations for the administration of pharmaceutical compounds are provided that comprise a therapeutically effective amount of a pharmaceutical compound, an organic solvent, and an oil. Lipophilic counterions, stabilizing agents and surfactants may also be included.		

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PHARMACEUTICAL COMPOSITIONS FOR ORAL ADMINISTRATION

This application is a continuation-in-part of copending U.S. Serial No. 07/307,385, filed February 6, 1989 which is a continuation-in-part of U.S. Serial No. 07/083,551, filed August 7, 1987.

TECHNICAL FIELD

This invention relates to liquid, solid or semisolid oral dosage forms for the administration of pharmaceutical compounds.

BACKGROUND OF THE INVENTION

Many pharmaceutical compounds that are very active when administered parenterally are poorly absorbed and relatively inactive when administered orally. For example, erythromycin antibiotics are highly effective against a variety of common pathogens and achieve high concentrations in tissues at infection sites, which further enhances their activity against intracellular pathogens, such as legionella. However, difficulty is experienced in achieving adequate bioavailability when administering these drugs orally due to their extremely bitter taste, their limited solubility in water, their susceptibility to acid degradation in the alimentary tract, and other factors well known to pharmaceutical chemists.

Peptides also have poor bioavailability when administered by nonparenteral routes due to their poor permeability through biological membranes. This may be due to

their large molecular size and their susceptibility to enzymatic or hydrolytic degradation in body fluids. Peptides are also readily ionizable.

Many approaches have been taken to increase the bioavailability of poorly absorbed drugs. For example, salts and esters of the base compound, taste masking agents, enteric and other coatings and rectal formulations have been used for erythromycin. Enamine derivatives have been disclosed in U.S. Patent Nos. 4,277,465 and 4,352,800 to promote absorption of therapeutically active substances. European Patent Application Nos. 131,228 and 245,126 disclose the use of N-methyl-2-pyrrolidone containing solvent systems for promoting percutaneous absorption of topical formulations. European Patent Application No. 275,404 discloses aerosol formulations of luteinizing hormone releasing hormone (LHRH) polypeptides that contain lipophilic counterions as solubilizing agents.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions for oral administration.

More particularly, the present invention relates to compositions for the oral administration of pharmaceutical compounds that comprise a therapeutically effective amount of a pharmaceutical compound, an organic solvent and an oil in a capsule. The compositions of the present invention may contain pharmaceutical compounds having ionizable groups such as free amines in peptides. For these compositions the formulation may also contain a stabilizing agent, a lipophilic counterion and a surfactant. The compositions of the present invention may also contain membrane penetrants, preservatives, emulsifiers, flavoring and coloring agents, antioxidants and buffers.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a graph that plots plasma LH response versus dose and compares a leuprolide composition of the present invention to intravenous and intraduodenal saline solutions of leuprolide.

FIGURE 2 is a graph that plots plasma concentration versus time and compares a tosufloxacin composition of the present invention to a conventional capsule composition;

FIGURE 3 is a graph that plots plasma concentration versus time and compares a progesterone composition of the present invention to a conventional tablet composition; and

FIGURE 4 is a graph that plots plasma concentration versus time and compares erythromycin compositions of the present invention to a conventional oral dosage form of erythromycin.

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a pharmaceutical compound, an organic solvent, and an oil. The compositions of the present invention may also contain a stabilizing agent, a lipophilic counterion and a surfactant.

As used herein the term "pharmaceutical compound" is intended to include any poorly absorbed drug such as antibiotics, as for example, erythromycin, doxorubicin, gentamicin or tosufloxacin and its salts such as tosylate, methane sulfonate, sulfate, and HCl; steroids, as for example dexamethasone; peptides, as for example, human growth hormone, bovine growth hormone including hormones, such as progesterone (which is also a steroid), or LHRH analogs such as p-Cl-Phe³-leuprolide, N-methyl-Ser⁴-D-Trp⁶-leuprolide, and leuprolide; peptidomimetics, for example, captopril, enalapril, and morphine; renin inhibitors, as for example, the H-((beta,

beta-dimethyl)-beta-Ala)-(4-OCH₃)-Phe-H amide of 2(5)-amino-1-cyclohexyl-3(R),4(S)-dihydroxy-6-methyl heptane and idebenone, a cerebral metabolic enhancer useful in the treatment of multiple sclerosis. When any of these drugs is utilized, it is intended to include the free base and its pharmaceutically acceptable salts, esters and derivatives. For example when the term "erythromycin" is used, it is intended to include the erythromycin 9-oximes, erythromycin 11,12-cyclic carbonates and 4'-deoxy-11,12-carbonates, 6-O-methyl-, 11-O-methyl-, and 6,11-di-O-methyl erythromycin, 8-fluoroerythromycin, erythromycin 11,12-cyclic carbamates, erythromycin 4'-carbamates, and compounds having various combinations of these structural modifications, as well as their pharmaceutically acceptable salts and esters.

As used herein the term "peptide" includes molecules built of amino acid building blocks which are linked together by amide bonds.

As used herein the term "peptidomimetic" includes those molecules which mimic the actions of a peptide but are not comprised of natural amino acid building blocks or do not contain amide bonds.

As used herein the term "oil" is intended to include triglyceride oils and other edible oils.

As used herein the term "triglyceride oil" is intended to include triglycerides which are liquid at room temperature (22°C) and consist primarily of triglycerides of C₆ to C₁₈ fatty acids such as capric, caproic, caprylic, stearic, palmitic, lauric, margaric, linoleic, linolenic and myristic acid. Oils such as olive oil and vegetable oil may be used as a source of triglyceride oils.

In addition to triglyceride oils, other edible oils containing aliphatic acid esters or mono- or di-esters of glycerol can also be used.

As used herein the term "lipophilic counterion" is intended to include organic acids or their salts having a pKa sufficiently low to render them ionizable at the formulation's pH. These acids include oleic acid, alkyl sulfonic acids, bile acids, salicylic acid, palmitic acid, and other aliphatic acids.

As used herein the term "surfactant" is intended to include nonionic surfactants such as mono and diglycerides, sorbitan fatty acid esters and ethers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitan esters and ethers, polyoxyethylene acids, polyoxyethylene alcohols and polyoxyethylene adducts.

As used herein the term "stabilizing agent" is intended to include polyelectrolytes such as polyethylene glycol, propylene glycol, sorbitol and glycerine.

Organic solvents that are useful in the compositions of the present invention include 2-pyrrolidone and its analogs, for example, N-methyl-2-pyrrolidone; alkyl acetates such as ethyl acetate and alcohols such as ethyl alcohol. The preferred organic solvent is 2-pyrrolidone or N-methyl-2-pyrrolidone.

As used herein the term "alkyl" is used to mean C₁-C₈ straight and branched chain radicals, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The compositions of the present invention will generally contain the following relative amounts of ingredients:

<u>Ingredient</u>	<u>Weight Percent</u>
pharmaceutical compound	0.01 - 50.00
organic solvent	0.50 - 95.00
oil	10.00 - 95.00
lipophilic counterion	0.000 - 20.00
surfactant	0.000 - 20.00
stabilizing agent	0.000 - 45.00

The preferred amounts of each ingredient of the compositions of the present invention are from about 1 to 25 weight percent pharmaceutical compound, 10 to 40 weight percent organic solvent, 30 to 80 weight percent oil, 15 to 25 weight percent stabilizing agent, and when the pharmaceutical compound has ionizable groups such as a free amine, 0.5 to 5 weight percent lipophilic counterion and 1 to 10 weight percent surfactant.

The compositions of the present invention can be utilized in soft or hard gelatin capsules. The capsules can be coated with a polymer such as cellulose acetate phthalate or hydroxypropylmethyl cellulose phthalate to resist the acidity of the stomach.

The compositions of the present invention can also be utilized in a variety of microencapsulation methods, as for example in the method described in CHEMTECH, Vol. 4, October, 1974, pp 623-636.

The capsule compositions of this invention may also desirably contain minor and pharmaceutically acceptable amounts of emulsifiers, flavoring and coloring agents, antioxidants, preservatives, buffers and like materials well known to the pharmaceutical chemist.

An especially preferred additive in the compositions of this invention is an essential oil. While not intending to be limited by theory, it appears that the inclusion of an essential oil or penetrant in the formulation alters the biokinetics of the dosage form, favoring more prompt absorption of the active drug. The result is an earlier and higher peak blood level for the drug and sustained subsequent blood levels. Preferred for use in the compositions of this invention are essential oils having from 6 to 12 carbon atoms, preferably from 8 to 12 carbon atoms. Such essential oils include, but are not limited to, eucalyptol, spearmint oil, peppermint oil, cinnamon oil, geraniol, geraniol acetate, and their synthetic equivalents.

The essential oil will preferably be incorporated in the compositions of this invention in an amount of about 25 mg. to about 750 mg., more preferably about 100 mg. to about 300 mg., most preferably about 150 mg. oil of peppermint per capsule. The capsule compositions of this invention will also preferably contain a pharmaceutically acceptable alcohol solvent for the combination, particularly if oil of peppermint is included in the composition.

One preferred class of the oils of the present invention, the triglyceride oils of mid-chain fatty acids, is represented by those oils which consist predominantly of glycerol triesters of C_6 to C_{10} fatty acids. Such oils can be prepared synthetically by well known techniques, or can be obtained from natural sources by known techniques of thermal or solvent fractionation of suitable natural oils, such as palm oil, to yield a fraction rich in the desired low-melting triglycerides. Such mid-chain fatty acid triglycerides are especially preferred because they have high solubility in and high absorptivity from digestive secretions, so that they improve dispersibility and absorption of the active drug compared with relatively high melting point triglyceride oils having substantial amounts of esters of C_{14} to C_{22} fatty acids. A preferred low melting, low molecular weight triglyceride oil is a low molecular weight fraction of palm oil which is rich in mixed esters of caprylic (octanoic) and capric (decanoic) acids. Such an oil is commercially available as NEOBEE® M-5 oil from PVO International, Inc. of Boonton, New Jersey. Other low melting cuts of palm oil are also suitable.

Another preferred class of triglyceride oils consists of triglyceride oils having a high percentage of glycerol triesters of unsaturated or polyunsaturated C_6 to C_{18} fatty acids. A preferred example of such an oil is safflower oil, which typically has a fatty acid composition of over 90% oleic

and linoleic acids or olive oil which has a glyceride composition of about 83.5% oleic acid, 9.4% palmitic acid, 4.0% linoleic acid, 2.0% stearic acid and 0.9% arachidic acid. Triglycerides of these acids are liquid at 20°C, while the corresponding saturated triglyceride tristearin is a waxy solid at room temperature and melts at about 72°C. Other low-melting vegetable oils or low-melting fractions of such oils obtained by conventional thermal or solvent fractionation are also suitable. While such unsaturated or polyunsaturated vegetable oils may offer a cost advantage in formulating compositions according to this invention, they also exhibit a greater tendency to oxidative deterioration, and may require the addition of oil soluble antioxidants, such as tocopherols. In addition, such oils are typically absorbed from the gastrointestinal tract in the form of chylomicrons, which may slow ultimate delivery of the active drug to the blood stream and thereby aid in the maintenance of sustained blood levels.

In some compositions according to this invention, the triglyceride oil may contain minor amounts of mono- and/or diglycerides to enhance solubility of the components or to enhance emulsification. In other compositions of this invention, depending upon the desires of the formulator, it will be preferable that the oil have a low polarity. In such a case, the preferred triglyceride oils will be low in content of mono- and diglycerides, as well as phospholipids, all of which have significant polarity.

Another component of a preferred embodiment of the present invention is a stabilizing agent, of which polyethylene glycol, propylene glycol, sorbitol and glycerine are examples. These polyelectrolytes may be added in an amount sufficient to improve the organoleptic qualities of the inventive composition. In particular, improvements in composition texture, dispersion integrity and viscosity may be obtained by the use of stabilizing agents. Such agents may additionally

provide steric stabilization of colloidal suspensions and, when a composition exhibits turbidity, may be used to improve clarity.

The ingredients of the compositions of the present invention can be incorporated into capsules in amounts well known to those of ordinary skill in the art. For example, when preparing capsules containing erythromycin, the triglyceride oil is preferably incorporated in the dosage forms of this invention in an amount of from about 75 mg. per capsule to about 750 mg. per capsule, more preferably about 200 mg. per capsule to about 500 mg. per capsule, most preferably about 300 mg. triglyceride oil per capsule containing, for example, about 250 mg. erythromycin base.

The most preferable organic solvent, N-methyl-2-pyrrolidone is incorporated into the composition preferably in an amount of from about 100 mg. to about 600 mg. per capsule, more preferably from about 150 mg. to about 300 mg. per capsule, most preferably about 200 mg.

N-methyl-2-pyrrolidone per capsule containing, for example, about 250 mg. erythromycin base. While not intending to be limited by theory, it is understood that the function of the N-methyl-2-pyrrolidone is to compensate for differences in polarity between the erythromycin antibiotic and the triglyceride oil solvent. In addition to promoting compatibility in the mixture, this compensation permits the erythromycin antibiotic to appear to cell membranes to be more solvent-like in character. Since the triglyceride oil solvent has good membrane permeability, this effect appears to enhance the membrane permeability of the erythromycin antibiotic, and thus improve bioavailability.

The invention will be more readily understood by the following nonlimiting examples.

EXAMPLE 1

Soft gelatin capsules of erythromycin base according to this invention are made as follows:

Capsule contents

13.6 grams of PEG fatty acid esters (Emulphor EL-719) are added to 50 grams of a low molecular weight palm oil fraction (NEOBEE® M-5) with stirring until the mixture is uniform. To this mixture is added 122.4 grams of N-methyl-2-pyrrolidone, and stirring is continued until the mixture is uniform. Into this mixture is added another 154 grams of the oil and the resulting liquid is mixed well. If it is desired to include an essential oil in the composition, that component is added along with the triglyceride oil. To this mixture is added approximately 180 grams of erythromycin base as the monohydrate, and the combination is mixed slowly until the erythromycin is completely dissolved, and then another 185.59 grams of erythromycin base monohydrate (to a total of 365.59 grams) is added. The solution is again mixed slowly until the erythromycin is completely dissolved, and then stirred at moderate speed until the solution is uniform. The resulting composition is assayed for potency and will yield approximately 1000 capsules containing 333 mg. erythromycin base each.

Gelatin capsules

131.5 grams of U.S.P. glycerin, 162.3 grams of sorbitol, 1.54 grams of methylparaben, NF and .39 grams of propylparaben, NF are combined with 280 grams of U.S.P. purified water with good mixing. The resulting mixture is cooled to 10°C with continued mixing, and the cooled mixture is blended with 425.5 grams gelatin, U.S.P. in a chilled blender. The resulting mass is melted at approximately 62°C under vacuum and held at that temperature for encapsulation.

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In forming the capsules a sufficient quantity of the erythromycin mixture is encapsulated to ensure that each capsule contains 333 mg. erythromycin by assay. The freshly molded capsules are washed and transferred to trays for drying. Following drying the capsules are inspected and culls are removed. The remaining capsules are washed with acetone, air dried and packaged.

If it is desired to provide the capsules with an enteric coating, a suitable polymer selected for its pH-dependent solubility is applied to the capsules. Selection and application of such polymer coatings is well known to the industrial pharmacist and by itself forms no part of the present invention. For example, in a typical procedure, 30 grams of hydroxypropylmethylcellulose phthalate (HPMCP) Type 55 is dissolved in 190 proof ethanol and U.S.P. purified water (distilled). An appropriate plasticizer for the HPMCP, such as 6 grams castor oil, is added to the solution with thorough mixing. The resulting mixture is applied to the capsules as prepared above in an air suspension coater at a rate of approximately 1 liter of enteric coating solution per kilogram of capsules. The coated capsules are then dried, inspected and packaged.

EXAMPLE 2

Three compositions were compared in conventional bioavailability studies in dogs. Formulations A and B were prepared in the general manner of EXAMPLE 1. Formulation C was a commercially available erythromycin tablet product providing good bioavailability.

FormulationComposition

A	Erythromycin base	250 mg.
soft gelatin	N-methyl-2-pyrrolidone	200 mg.
capsules	NEOBEE® M-5 oil	300 mg.
(enteric coated)	Ethanol	20 mg.
B	Erythromycin base	250 mg.
soft gelatin	N-methyl-2-pyrrolidone	200 mg.
capsules	NEOBEE® M-5 oil	180 mg.
(enteric coated)	Peppermint oil	150 mg.
	Ethanol	20 mg.
C	commercial capsules of enteric coated erythromycin particles containing erythromycin 250 mg. per tablet (PCE®, Abbott Laboratories)	

Formulations A and B were prepared by the procedure described in EXAMPLE 1. Formulation C is available from Abbott Laboratories.

After overnight fasting, histamine was injected into each dog to stimulate gastric acid secretion, followed in one hour by the appropriate formulation. Blood samples were obtained periodically for 12 hours and assayed for active drug by a standard microbiological method. Variability of the data was within normal limits and no non-absorbers were found in any of the test groups. As shown in TABLE 1, results from these studies demonstrate an approximate two-fold improvement in oral availability of erythromycin base when compared to a leading erythromycin tablet product as control.

TABLE 1

<u>Formulation</u>	<u>T_{max}[*]</u> <u>(hr)</u>	<u>Mean + S.D.</u>	
		<u>C_{max}^{**}</u> <u>(ug/ml)</u>	<u>AUC^{***}</u> <u>(ug/ml x hr)</u>
A	1.67 ± 0.47	2.7 ± 1.0	9.5 ± 4.5
B	1.33 ± 0.47	3.3 ± 0.6	9.0 ± 2.8
C	1.80 ± 0.40	1.9 ± 0.5	4.5 ± 1.3

* T_{max} = Time from administration of compound until maximum plasma concentration is achieved.

** C_{max} = Maximum plasma concentration of administered compound.

*** AUC = The area under the plasma level versus time curve (area under the curve).

EXAMPLE 3

A composition was prepared that contained the following ingredients:

<u>Ingredient</u>	<u>Weight Percent</u>
leuprolide acetate	1.00 gm.
olive oil	33.00 gm.
N-methyl-2-pyrrolidone	46.00 gm.
oleic acid	0.80 gm.
peppermint oil	10.00 gm.
surfactant, Emulphor*	5.00 gm.
water/alcohol	4.20 gm.

* Emulphor is available from GAF Corp., Wayne, N.J.

The leuprolide acetate was dissolved in a small amount of water-alcohol mixture containing oleic acid. Surfactant was

added and carefully mixed until a uniform colloidal dispersion was formed. This dispersion was added to a flask containing N-methyl-2-pyrrolidone and olive oil and mixed until a uniform dispersion was formed.

The composition was evaluated against saline solutions of leuprolide acetate by a procedure in which male Sprague/Dawley rats (about 200g) were castrated and shipped 3 weeks post surgery. These rats were used at about 5 weeks after surgery, at approximately 350-450g body weight, and had 10- to 20-fold elevated basal plasma luteinizing hormone (LH) levels compared to intact rats. Compounds were administered as a single bolus dose by the intravenous (jugular), intraduodenal, and oral routes under light ether anesthesia. Plasma LH concentration was determined by a radio-immunoassay procedure (RIA) as described below. Blood samples were obtained by jugular venipuncture before dosing, and except where otherwise noted, at 30, 60, 90, 120, 180, 240 and 360 minutes. Blood was withdrawn into 1 cc tuberculin syringes prewet with 15% tripotassium EDTA. Plasma was obtained by centrifugation at ~~5000 rpm for 15 minutes.~~

For evaluation of the plasma concentration of the administered compound, the bleeding schedule was adjusted to include an additional early bleeding at 10 minutes, and terminated at 180 minutes. Compounds were administered intravenously and intraduodenally, and the concentration of compound was determined in timed blood samples by RIA. The areas under the blood level vs time curves were calculated for both routes, and the intraduodenal bioavailability calculated with the equation:

$$F = \frac{\text{AUC}_{\text{ID}}}{\text{AUC}_{\text{IV}}} \times \frac{\text{Dose}_{\text{IV}}}{\text{Dose}_{\text{ID}}} \times 100$$

where F is the percent bioavailability.

In carrying out the RIA procedure of the plasma samples, ovine LH was iodinated using the Chloramine-T method, and purified by Sephadex G-75 gel chromatography. The standard curve was constructed with the national standard rat LH preparation (NIH-RP2). 60 uL of each rat plasma sample was diluted to 400 uL with 2.5% normal rabbit serum in Dulbecco's phosphate buffered saline (NRS/PBS; pH 7.4). 100 uL of the diluted sample (containing 15 uL plasma) was diluted to 400 uL with Medium 199 buffer (Medium 199, Hepes 10 mM pH adjusted to 7.4 with sodium hydroxide, bovine serum albumin 0.3%, gentamicin 0.01% and sodium azide 0.01%), and combined with 100 uL of ^{125}I -LH (20000 cpm) and 100 uL antibody. The mixture was incubated overnight (18-24 hours) at 4°C. 200 uL of NRS/PBS was added to the mixture, followed by 75 uL of goat-antirabbit antibody. After 4 hours at 4°C, antibody-bound ^{125}I -LH was precipitated by centrifugation at 2300 rcf for 20 minutes, and counted by gamma spectroscopy. Each sample was assayed in triplicate. The sensitivity of the assay was 50 picograms (pg) per tube, and range was 50 to 6000 pg. Plasma LH responses, which appear to be log-normally distributed, have been summarized as an integrated response over time ($\log[\text{response LH} / \text{control LH}] \text{ min}$), using the trapezoidal rule. The dose of leuprolide which produced a 50% of maximum LH response (ED_{50}) was calculated from the best fit of the function:

$$\text{LH response} = \frac{\text{maximum AUC} \times \text{Dose}}{(\text{AUC}) \quad \text{ED}_{50} + \text{Dose}}$$

Leuprolide was labelled with ^{125}I via Chloramine-T oxidation and purified via ion exchange chromatography. An antibody to LHRH analog which recognized the tripeptide antigenic determinant x-Leu-Arg-Pro-NH₂ was utilized. This antibody appeared to cross-react with a number of LHRH analogs, including leuprolide ($\text{EC}_{50} = 100 \text{ pg}$); the limit of

detectability for leuprolide was approximately 10 pg/sample. The RIA was conducted in a similar manner to the LH RIA, but 15000 cpm of ^{125}I -[Tyr⁵]leuprolide was utilized as the tracer. A separate standard curve was constructed with serial dilutions of leuprolide from 5 to 25000 pg per tube.

FIGURE 1 is a graph that plots plasma LH response versus dose and compares a leuprolide composition of the present invention to intravenous and intraduodenal saline solutions of leuprolide.

TABLE 2 below demonstrates the improvement in bioavailability of intraduodenal doses of the leuprolide acetate formulations of the present invention when compared to leuprolide acetate in saline.

TABLE 2

Bioavailability of Intraduodenally and Orally
Administered Leuprolide from Oil Dispersion
Formulation in Rats

<u>Dose*</u> <u>(ug/kg)</u>	<u>Route</u>	<u>Vehicle</u>	<u>AUC</u> <u>(ng/ml min)</u>	<u>Bioavail-</u> <u>ability vs</u> <u>IV route (%)</u>	<u>Relative</u> <u>Bioavail-</u> <u>ability</u>
100	IV	saline	11180.2 \pm 852.7	100	--
3000	ID	saline	274.0 \pm 64.7	.082	1
100	ID	oil formu- lation	758.5 \pm 473.6	6.8	83.0
1000	ID	oil formu- lation	3790.8 \pm 2030.1	3.4	41.5
10000	ID	oil formu- lation	63772.1 \pm 17941	5.7	69.8
1000	PO	oil formu- lation	1020.2 \pm 662.0	0.9	11.2

- * Doses have not been corrected for recovery of leuprolide which was generally 50-85% of the theoretical value.

TABLE 3 below shows the apparent bioavailability of leuprolide formulations as deduced from the relative LH responses in castrate male rats.

TABLE 3

<u>Route</u>	<u>Dose Range</u> <u>ug/kg</u>	<u>Vehicle</u>	<u>ED₅₀</u> [*] <u>ug/kg</u>	<u>Potency</u> <u>Relative</u> <u>to IV Dose</u>
IV	0.01-100	saline	0.14	100%
ID	10-1000	saline	59.0	0.28%
ID	1-100	oil		
		formulation	1.25	11.1%

- * Effective dose to elicit 50% of maximal effect of the drug.

EXAMPLE 4

Compositions containing leuprolide acetate were further prepared using the formulations shown below, and were tested on dogs, monkeys and rats as shown in TABLES 4-6. Formulation C was found to be especially representative of the leuprolide-containing compositions of the present invention.

Formulation A

water	2.00 ml.
decane sulfonate, Na salt	0.24 gm.
leuprolide acetate	0.30 gm.
peppermint oil	10.00 gm.
N-methyl-2-pyrrolidone	35.00 ml.
Emulphor® EL719	10.00 ml.
olive oil	q.s. to 100 ml.

Formulation B

water	2.00 ml.
decane sulfonate, Na salt	0.24 gm.
dehydrochloric acid	1.00 gm.
leuprolide acetate	0.30 gm.
menthol, USP, crystalline	1.00 gm.
N-methyl-2-pyrrolidone	25.00 ml.
Emulphor® EL719	10.00 ml.
olive oil	q.s. to 100 ml.

Formulation C

water	2.00 ml.
decane sulfonate, Na salt	0.24 gm.
polyethylene glycol	10.00 ml.
propylene glycol	10.00 ml.
leuprolide acetate	0.30 gm.
peppermint oil	10.00 gm.
N-methyl -2- pyrrolidone	35.00 ml.
Emulphor® EL719	10.00 ml.
olive oil	q.s. to 100 ml.

The above formulations were tested for bioavailability using procedures identical or comparable to those of EXAMPLE 3.

above. The inventive compositions were administered intraduodenally (ID) to rats via direct injection using a 30 gauge needle, and to dogs and monkeys via endoscope. TABLES 4-6 show the results obtained in dogs, monkeys and rats, respectively.

TABLE 4

Absorption of Leuprolide Acetate from
the Duodenum of Dogs

<u>Formulation</u>	<u>Dose*</u> ($\mu\text{g}/\text{kg}$)	<u>Route</u>	<u>AUC</u> ($\mu\text{g}/\text{ml.} \times \text{min.}$)	<u>Bioavailability</u> vs. IV route %
saline	500	ID	1.01 ± 0.19	1.15
A	500	ID	3.09 ± 0.98	4.42
B	500	ID	0.89 ± 0.12	1.01
saline	100	IV	17.65 ± 1.86	(100)

TABLE 5

Absorption of Leuprolide Acetate from
the Duodenum of Monkeys

<u>Formulation</u>	<u>Dose*</u> ($\mu\text{g}/\text{kg}$)	<u>Route</u>	<u>AUC</u> ($\mu\text{g}/\text{ml.} \times \text{min.}$)	<u>Bioavailability</u> vs. IV route %
saline	1667	ID	3.41 ± 1.29	0.73
A	1667	ID	10.42 ± 1.05	2.23
B	1667	ID	1.24 ± 0.10	0.26
saline	333	IV	93.19 ± 18.12	(100)

TABLE 6

Absorption of Leuprolide Acetate from
the Duodenum of Rat

<u>Formulation</u>	<u>Dose*</u> ($\mu\text{g/kg}$)	<u>Route</u>	<u>AUC</u> ($\mu\text{g/ml.} \times \text{min.}$)	<u>Bioavailability</u> vs. IV route %
saline	3000	ID	0.23 ± 0.06	0.14
A	10000	ID	35.94 ± 4.35	6.86
B	10000	ID	25.67 ± 16.26	4.90
C	333	IV	7.63 ± 1.81	4.85
saline	1000	IV	52.42 ± 3.35	(100)

* Doses not corrected for recovery of leuprolide.

EXAMPLE 5

FIGURE 2 is a graph that plots plasma concentration versus time and compares a tosufloxacin composition of the present invention to a conventional tablet formulation which is an encapsulated form of tosufloxacin tosylate powder.

The tosufloxacin composition contained the following ingredients:

<u>Ingredient</u>	<u>Percent</u>
Tosufloxacin tosylate	10.00 gm.
N-methyl-2-pyrrolidone	q.s.* 100 ml.

* q.s. = adjust volume to indicated value

The tosylate salt of tosufloxacin was added to N-methyl-2-pyrrolidone and mixed for approximately five minutes until completely dissolved, then the total volume was brought up

to the desired volume. Capsules were prepared from this composition and from a control formulation which contained only powdered tosufloxacin tosylate.

The capsules which contained sufficient quantities of each tosufloxacin formulation to deliver approximately 14.27 mg/kg of tosufloxacin tosylate were administered to beagle dogs. The dogs were fasted for at least twelve hours and given a histamine pretreatment of 0.1 mg/kg of a 1.0 mg/ml solution to stimulate gastric activity. Blood sampling was done at 0, 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours after capsule administration. 2.5 ml plasma samples were heparinized and assayed microbiologically by a procedure in which an appropriate quantity of a sterilized Antibiotic Medium containing:

Antibiotic Medium

Celitate peptone	6.0 g
Trypticase peptone	4.0 g
Yeast extract	3.0 g
Beef extract	1.5 g
Dextrose	1.0 g
Agar	15.0 g
Distilled water	1.0 liter
pH	6.6 \pm 0.2

is cooled from autoclave temperature to 8°C \pm 1°C, the pH is adjusted to pH 8.0, and seed culture of B. subtilis ATCC 6633 is added to the medium.

The seeded medium is evenly dispensed into the desired number of sterile plastic petri dishes (243 x 243 x 18 mm) 90 to 100 ml/plate and the plates are set to harden on a level bench top. They are then inverted and refrigerated for a minimum of 30 minutes until ready to use.

The assay plates are spiked with plasmas containing known and unknown concentrations of tosufloxacin and are then incubated at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ overnight. The zones of inhibition are measured to the nearest 0.5 mm by the Optomax Zone Reader (Optomax, Inc.). The data are transferred to the DEC-10 computer in random order and plasma calculations are made.

FIGURE 2 demonstrates the improvements in plasma concentration achieved by the tosufloxacin compositions of the present invention.

EXAMPLE 6

FIGURE 3 is a graph that plots plasma concentration versus time and compares a progesterone composition of the present invention versus a commercial capsule composition which was used as a control.

The control capsule formulation marketed by Besins-Iscovesco Laboratories of France under the trademark Utrogestan, contains 100 mg of micronized progesterone in peanut oil. The progesterone formulation of the present invention contains the following ingredients:

<u>Ingredient</u>	<u>Amount</u>
Alcohol	3.00 ml
NEOBEE® M5 oil	40.00 ml
N-methyl-2-pyrrolidone	55.00 ml
Emulphor EL-719*	0.30 gm
Progesterone	15.00 gm

*available from GAF Corp., Wayne N.J.

The progesterone formulation of the present invention was prepared by adding ethyl alcohol to the Neobee oil and mixing until uniform. The N-methyl-2-pyrrolidone was mixed into the emulphor in a separate container until uniform. The progesterone was then added to the N-methyl-2-pyrrolidone solution and mixed until it dissolved. The alcohol-Neobee mixture was then added to the progesterone solution and mixed well to form a uniform homogeneous solution. Appropriate amounts of this progesterone solution were filled into gelatin capsules so that each capsule contained 100 mg progesterone.

Eight beagle dogs each weighing approximately 10 kilograms were fasted for at least 12 hours. Each dog was then given one capsule and blood samples drawn at 0, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0, 10.0 and 24.0 hours post dosing. Plasma from these samples were removed, heparinized, and assayed by HPLC for progesterone levels. The respective blood level data are plotted in FIGURE 3 as a function of time. This graph demonstrates the improvements in plasma concentration achieved by the progesterone compositions of the present invention. TABLE 7 summarizes the bioavailability result obtained from this study. The table demonstrates the improvements in the bioavailability of progesterone compositions when they are administered in composition of the present invention.

TABLE 4

PROGESTERONE DATA IN MALE BEAGLE DOGS

<u>Product</u>	<u>T_{max}</u> <u>(hrs)</u>	<u>C_{max}</u> <u>(ng/ml)</u>	<u>AUC</u> <u>(ng/ml.hr)</u>	<u>Relative</u> <u>Bioavailability</u>
progesterone SEC oil solution 100 mg	0.25	253.95	254.5	4

Progesterone

100 mg

(Utrogestan) 1.00 11.10 63.0 1

EXAMPLE 7

FIGURE 4 is a graph that plots plasma concentration versus time data generated in male beagle dogs and compares erythromycin compositions of the present invention with and without peppermint oil versus particle coated erythromycin (PCE®), an oral dosage form of erythromycin.

The erythromycin compositions and test procedures utilized in this example are identical to those utilized in EXAMPLE 2.

This graph demonstrates the improvements in plasma concentration achieved by the erythromycin compositions of the present invention.

EXAMPLE 8

Comparative bioavailability studies in fasted and non-fasted normal male humans were conducted to compare the bioavailability of erythromycin compositions of the present invention (erythromycin base soft elastic capsule (SEC) oil solution) to erythromycin base tablets.

Fourteen (14) healthy adult males were used in this study. The formulations were assigned to these subjects in a randomized protocol. In the study, subjects were fasted from all food and beverage, except for water to quench thirst and scheduled meals, for a minimum of twelve hours prior to dosing until after the 6-hours blood collection on each dosing day. Oral temperature, sitting blood pressure, and sitting pulse were measured for each subject prior to each dosing.

On the first dosing day in each period (fasting regimen), breakfast was served following the 2-hour blood collection. On the second dosing day in each period (nonfasting regimen), breakfast was served one-half hour prior to dosing. Lunch was served following the 4.5-hour blood collection on all dosing days. All meals were standardized and consumed within 20 to 25 minutes. The breakfasts were started at times which would ensure that the time intervals relative to dosing were the same for all subjects.

Blood Collection

Seven (7) ml blood samples were collected by venipuncture prior to dosing (0 hour) and at the following times after dosing on each dosing day: 1, 2, 3, 4, 6, 8, 11 and 12 hours. Serum from these samples were assayed for erythromycin activity using a microbiological method similar to the method published by Bell, Hamman, and Grundy (Applied Microbiology, 17:88, 1969).

The data are presented in TABLES 8 and 9 respectively.

TABLE 8

Data in Fasted Normal Male Humans

<u>Product</u>	<u>T_{max}</u> <u>hrs</u>	<u>C_{max}</u> <u>mcg/ml</u>	<u>AUC</u>	<u>%</u> <u>C.V.*</u>
Erythromycin Base SEC oil solution, 250 mg	2.3	1.52	4.28(5.70)	44
Erythromycin Base Tablet, PCE®, 333 mg	2.8	1.46	4.79	28

* Covariance = The percent variability within all of the subjects tested.

TABLE 9

Comparative Bioavailability of Erythromycin Base
Data in Non-fasted Normal Male Humans

<u>Product</u>	<u>T_{max}</u> <u>hrs</u>	<u>C_{max}</u> <u>mcg/ml</u>	<u>AUC</u>	<u>%</u> <u>C.V.</u>
Erythromycin Base SEC oil solution, 250 mg	6.6	0.86	2.64(3.52)	69
Erythromycin Base Tablet, PCE®, 333 mg	5.5	0.78	2.62	35

Dose of product corrected to agree with Control
formulation (PCE®, 333 mg).

EXAMPLE 9

A leuprolide composition was prepared using ethyl alcohol as the organic solvent and following the general procedure described in EXAMPLE 1. The composition contained the following ingredients:

<u>Ingredient</u>	<u>Weight Percent</u>
leuprolide acetate	0.80 gm.
Neobee® oil	49.90 gm.
ethanol	43.50 gm.
oleic acid	0.80 gm.
surfactant (Emulphor®)	5.00 gm.

In TABLE 10, the bioavailability of leuprolide from the formulation of EXAMPLE 8 was determined after duodenal administration, and compared with leuprolide in saline solution following the general analysis discussed in EXAMPLE 3.

TABLE 10

	Dose		AUC*	Relative	Fold
<u>Route</u>	<u>ug/kg</u>	<u>Vehicle</u>	<u>ng/ml min</u>	<u>Bioavailability</u>	<u>Improvement</u>
ID	3000	saline	274.0	0.082	1
ID	8000	formulation	27556.6	3.08	38

*AUC corrected for recovery of leuprolide acetate from vehicle.

This invention has been described in terms of specific embodiments set forth in detail. It should be understood, however, that these embodiments are presented by way of illustration only, and that the invention is not necessarily limited thereto. Modifications and variations within the spirit and scope of the claims that follow will be readily apparent from this disclosure, as those skilled in the art will appreciate.

CLAIMS

1. A composition for the oral administration of pharmaceutical compounds that comprises a therapeutically effective amount of a pharmaceutical compound, an organic solvent, and an oil.

2. A composition according to Claim 1 wherein the organic solvent is selected from the group consisting of a 2-pyrrolidone and an alcohol.

3. A composition according to Claim 2 wherein the 2-pyrrolidone is N-methyl-2-pyrrolidone.

4. A composition according to Claim 1 wherein the pharmaceutical compound is selected from the group consisting of antibiotic, steroid, peptide, hormone, LHRH analog, peptidomimetic, quinolone, and renin inhibitor.

5. A composition according to Claim 4 wherein the antibiotic is an erythromycin compound, the LHRH analog is leuprolide, the hormone is progesterone, and the quinolone is tosufloxacin.

6. A composition according to Claim 5 wherein the erythromycin compound is selected from erythromycin base, 6-O-methyl erythromycin, and pharmaceutically acceptable salts and esters thereof.

7. A composition according to Claim 1 which further comprises a surfactant.

8. A composition according to Claim 1 which further comprises a lipophilic counterion and a surfactant.

9. A composition according to Claim 8 wherein the lipophilic counterion is selected from the group consisting of oleic acid, alkyl sulfonic acids, bile acids, salicylic acid, and palmitic acid.

10. A composition according to Claim 1 wherein the oil is a low melting triglyceride oil having a low molecular weight fraction of palm oil comprising mixed esters of caprylic and capric acids.

11. A composition according to Claim 1 which further comprises a pharmaceutically acceptable C_6 to C_{12} essential oil.

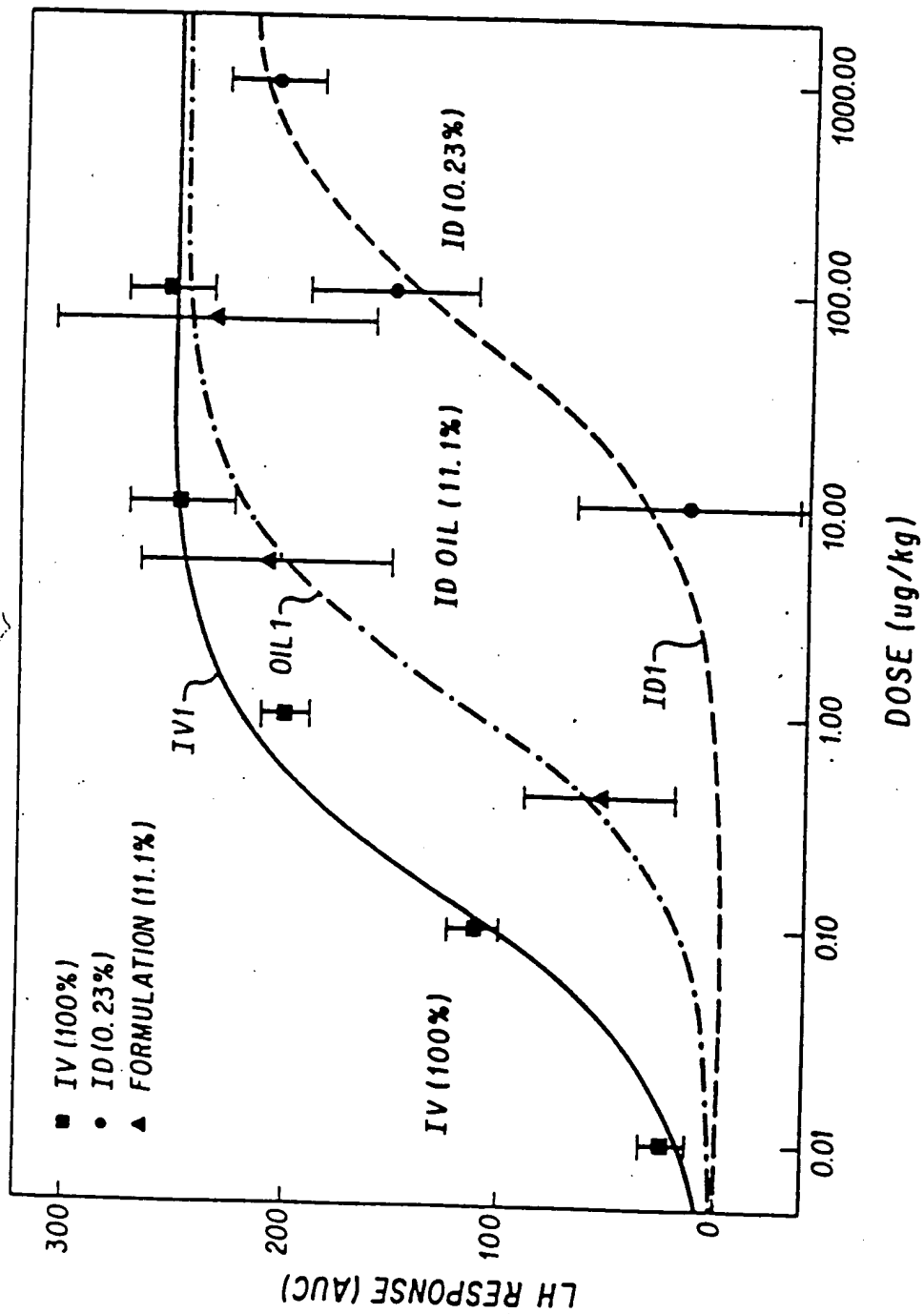
12. A composition according to Claim 11 in which the essential oil is selected from the group consisting of oil of peppermint, oil of cinnamon, oil of spearmint, eucalyptol, geraniol, geraniol acetate, and synthetic equivalents thereof.

13. A composition according to Claim 7 which further comprises a stabilizing agent.

14. A composition according to Claim 13 in which the stabilizing agent is selected from the group consisting of polyethylene glycol, proylene glycol, sorbitol and glycerine.

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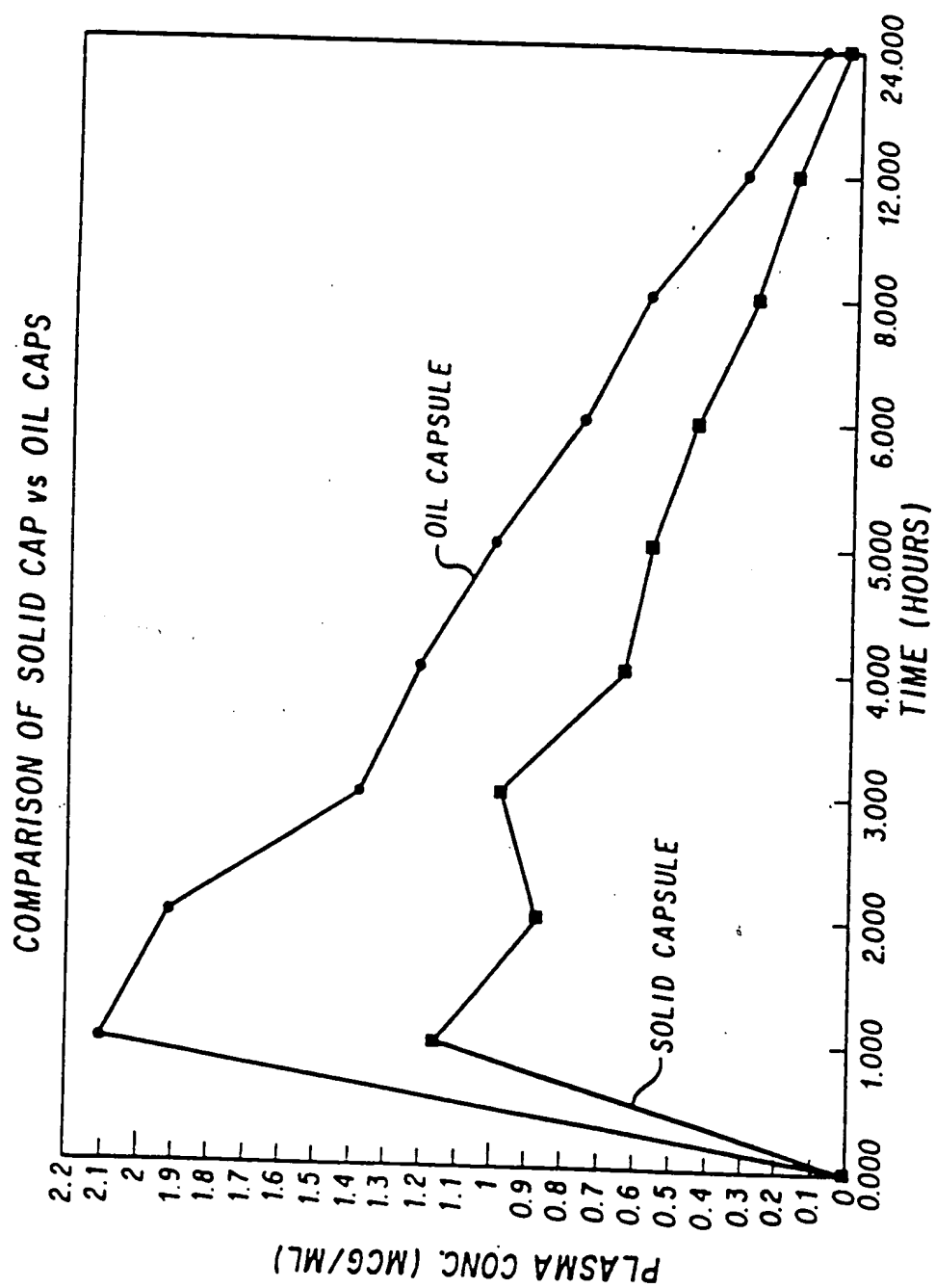


FORMULATION INCREASES DUODENAL BIOAVAILABILITY OF LEUPROLIDE
FIG. 1

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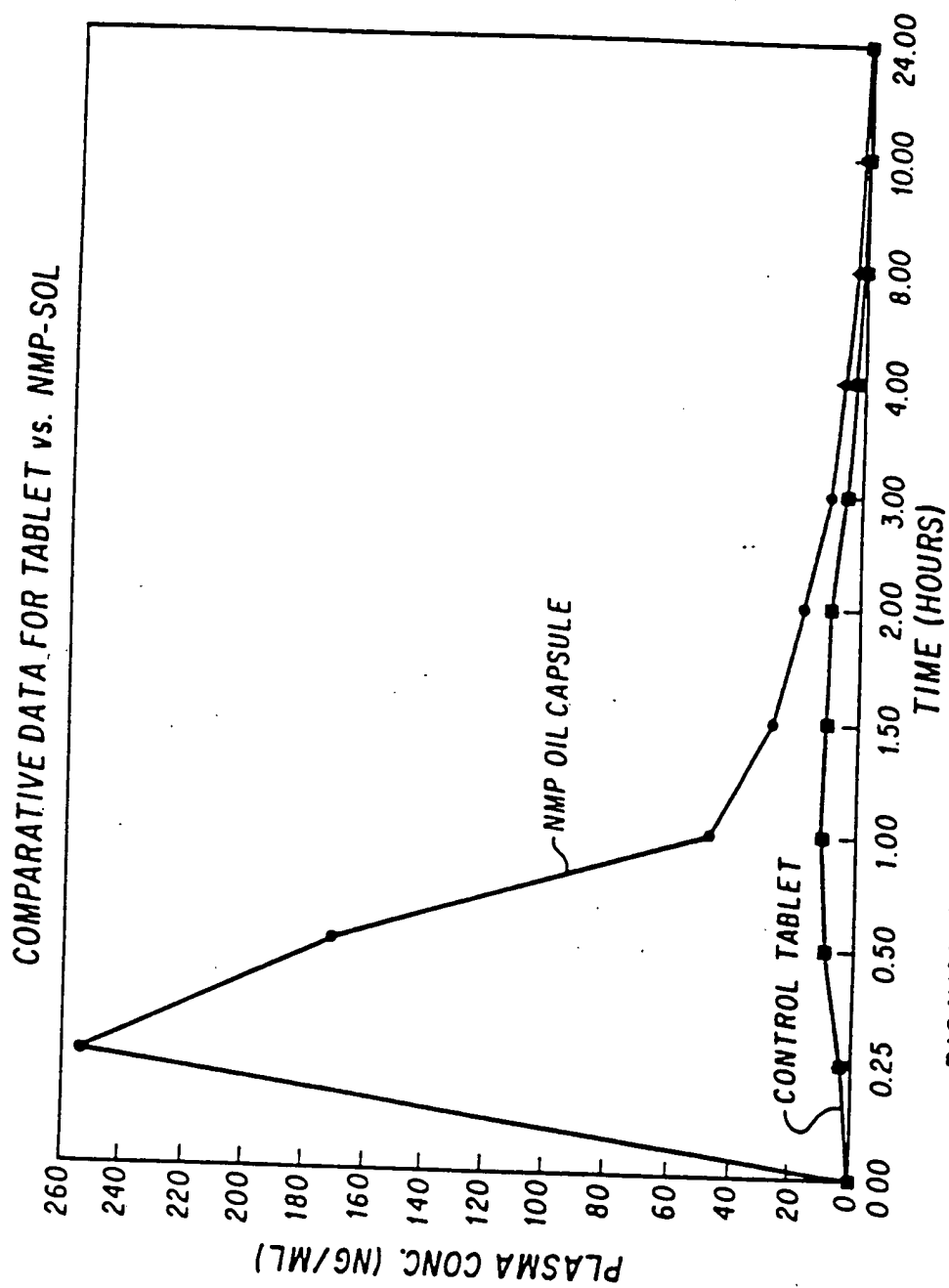


BIOAVAILABILITY OF TOSUFLOXACIN IN DOGS
FIG. 2

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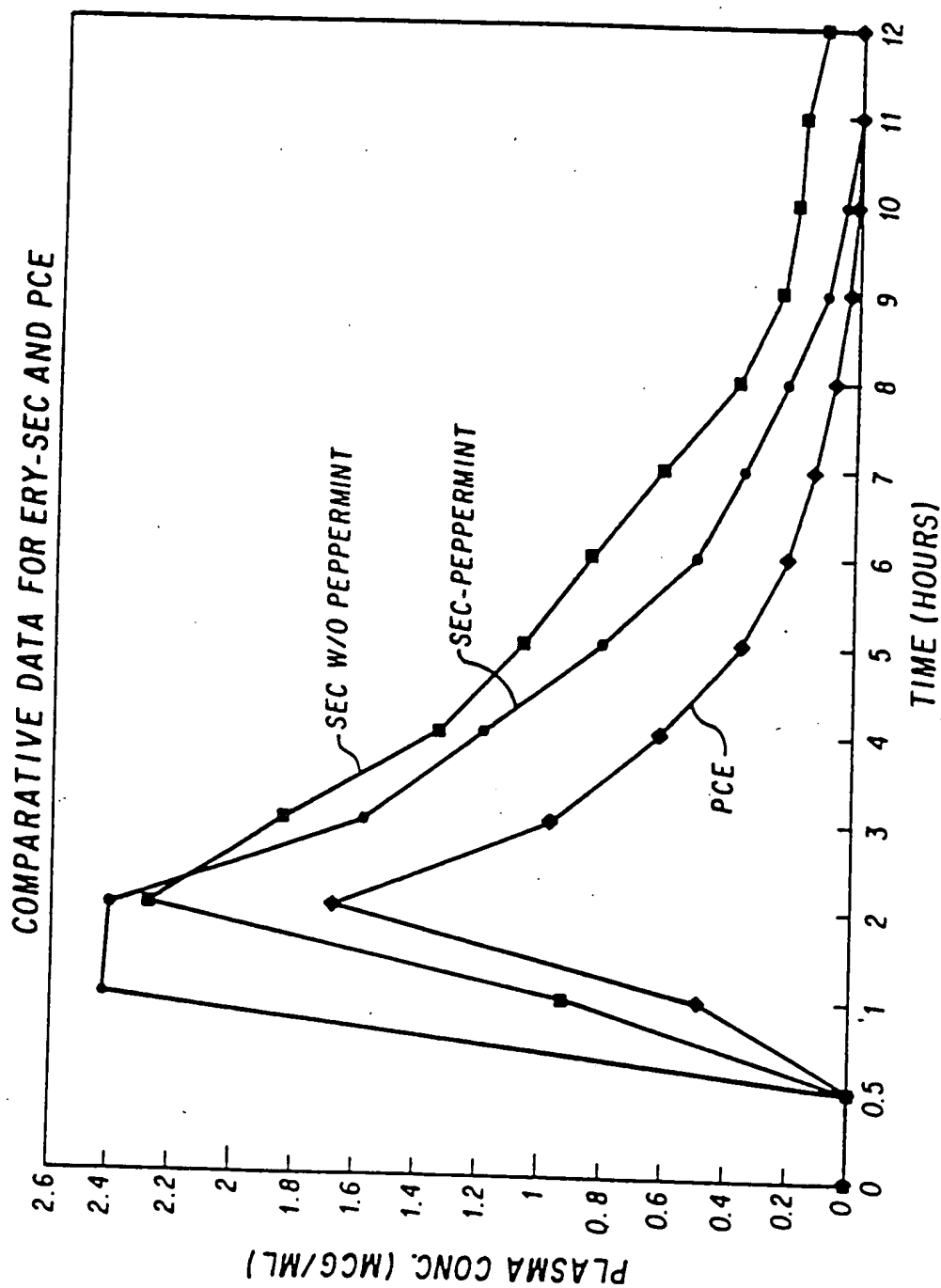
BIOAVAILABILITY OF PROGESTERONE IN DOGS

FIG. 3

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BIOAVAILABILITY OF ERYTHROMYCIN BASE
FIG. 4

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/00721

I. CLASSIFICATION OF SUBJECT MATTER (In several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5) A61K 31/00, 47/00 U.S. CL. 514/15, 21, 29, 34, 38, 40, 177, 277, 408, 424, 800		
II. FIELDS SEARCHED		
Minimum Documentation Searched ?		
Classification System	Classification Symbols	
U.S.	514/15, 21, 29, 34, 38, 40, 177, 277, 408, 424, 800	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages †	Relevant to Claim No. ‡
X	US, A, 4,150,128 (JASIONOWSKI) 17 April 1979, see column 2, lines 26-65	1-14
Y	US, A, 4,612,364 (YAMAMOTO ET AL) 16 September 1986, see column 6, lines 10-22	11-14
X	US, A, Re.32,534 (YANAIMARA ET AL) 27 October 1987, see column 6, lines 11-66	
X P	US, A, 4,857,506 (TYLE) 15 August 1989, see column 2, lines 15-48	1-14
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: †</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application, cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step if the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
05 April 1990		08 MAY 1990
International Searching Authority		Signature of Authorized Officer
ISA/US		Elli Peselov

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